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Deoxygenative Borylation of Secondary and Tertiary Alcohols

Florian W. Friese^[a] and Armido Studer*^[a]

Abstract: Two different approaches for the deoxygenative radical borylation of secondary and tertiary alcohols are presented. These transformations proceed either via a metal-free silyl radical mediated pathway or utilize visible light photoredox catalysis. Readily available xanthates or methyl oxalates are used as radical precursors. Reactions that show broad substrate scope and high functional group tolerance are conducted under mild and practical conditions.

Alkyl boronic esters are highly valuable building blocks in chemical synthesis since the C-B-bond is easily transformed into a great variety of useful functional groups. Moreover, these boronic esters are good substrates in transition-metal catalyzed C-C coupling reactions.^[1] Therefore, synthetic methods for their preparation are demanded. Along these lines, protocols for the borylation of alkyl halides^[2], carboxylic acids^[3] and amines^[4] using diboron reagents by applying either radical chemistry or transition-metal catalysis have been reported recently (Scheme 1, A-C). Surprisingly, despite the easy accessibility and large abundance of alcohols, their deoxygenative borylation remains underdeveloped. Metal-catalyzed borylation of primary and secondary alkyl tosylates was disclosed^[5,2i] but borylation of tertiary alcohols is unknown to our knowledge.

We therefore decided to focus on the deoxygenative borylation of secondary and tertiary alcohols using a radical approach. The borylation of alkyl radicals by B₂cat₂ in the presence of a Lewis base (commonly an amide used as the solvent) has already been documented to be a very efficient reaction.^[2h,3a,6] Encouraged by these studies, we envisioned a similar radical strategy using a suitable alcohol activating group and show herein that xanthates, readily prepared from alcohols and widely applied in the Barton-McCombie deoxygenation reaction,^[7] can be converted to the corresponding alkyl boronic esters using silanes as radical mediators (Scheme 1D). Since tertiary xanthates are not stable, we also introduce a second protocol to prepare tertiary alkyl boronic esters from easily accessible tert-alkyl oxalates^[8] using redox catalysis.

Borylation of xanthates was studied first. It is well known that silanes can act as radical chain reducing reagents for the reduction of xanthates.^[9] In contrast to tin hydrides, they are nontoxic and the rate constant k for the reduction of a C-radical by a silane is 2 to 3 orders of magnitude smaller than the k-value for the same reduction with a tin hydride. Moreover, from our previous studies we knew that the C-radical borylation with B₂cat₂ is a very fast transformation^[2h] that should outcompete the direct

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slower C-radical reduction by a silane. Therefore, silanes were considered as radical mediators in the targeted deoxygenative borylation.

A) Borylation of alkyl halides





C) Deaminative borylation



D) Deoxygenative borylation (this study)

diboron reagents

bis(catecholato)diboron).



secondary, tertiary Scheme 1. Borylation of alkyl halides, carboxylic acids, amines and alcohols = bis(pinacolato)diboron, (B₂pin₂ B₂cat₂

Xanthate 1a, selected as the model substrate, was reacted with B₂cat₂ in DMF using AIBN in the presence of different silanes at 70 °C. Reaction optimization revealed that the best result is obtained upon usina commercial TTMSS (tris(trimethylsilyl)silane)^[9] as the reducing reagent. With Ph₃SiH, Ph₂MeSiH and Ph₂SiH₂, deoxygenative borylation did not occur. We also found that the xanthate functionality as compared to the thionocarbamate (X = imidazolyl, see Scheme 1D) or thionocarbonate (X = OPh) entity is the best C-radical precursor for this transformation. Notably, a radical chain is likely not operating and the highest yield was achieved by using a stoichiometric amount of AIBN at 70 °C in DMF (see supplementary material (SI)). The competing direct alkyl radical reduction by TTMSS was prevented by using the diboron reagent in excess (4.0 equiv). Due to the instability of the catechol boronic ester, the crude product was transesterified with pinacol and Et₃N to give the alkyl boronic ester 3a in 88% isolated yield (method A,

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Scheme 2). Reducing the amount of B_2cat_2 to 2 equiv led to a slightly lower yield (75%, see Table S1) and therefore all further experiments were conducted using 4 equiv of the diborane.

Method A:



Scheme 2. Method A: Deoxygenative borylation of alkyl xanthates using AIBN/TTMSS. Reaction conditions: **1ai** (0.2 mmol), B_2cat_2 (0.8 mmol), TTMSS (0.23 mmol), AIBN (0.2 mmol), DMF (0.6 mL), 70 °C, 15 h; pinacol (0.8 mmol), Et₃N (0.7 mL), 1h, isolated yields. Method B: Light-mediated borylation. Reaction conditions: **1j-n** (0.2 mmol), B_2cat_2 (0.8 mmol), TTMSS (0.23 mmol), DMAc (0.6 mL, + dioxane in some cases, see SI), 35 °C, 24-48 h; pinacol (0.8 mmol), Et₃N (0.7 mL), 1h, isolated yields; ^areaction was performed on a 1.0 mmol scale.

Under optimized conditions, the secondary alcohol-derived xanthates **1b**, **1d** and **1e** were successfully borylated using method A (**3b**, **d**, **e**, 63-67%). The tertiary adamantyl xanthate **1c**, that cannot undergo *syn*-elimination, was an eligible substrate to provide **3c** in 63% yield. Notably, deoxygenative borylation of *L*-menthol (**3f**) and isoborneol (**3g**) was accomplished with complete stereocontrol. The reaction tolerates internal alkenes and ester moieties as both cholesterol and lithocholic acid methyl ester were borylated with good to excellent diastereoselectivity (**3h**, **i**). The relative stereochemistry was assigned by oxidation and subsequent NMR-experiments (see SI). The scalability was evaluated by performing the reaction on a 1.0 mmol scale providing **3a** in 83% yield.

During these investigations, we realized that irradiation of the reaction mixture with blue LEDs in the absence of AIBN in DMAc also allowed accessing the borylated products in good to excellent yields (method B). Moreover, if the synthesis of the xanthate derivative is challenging (e.g. for ketones **3**I,**n**), the corresponding O-thionocarbamate has to be selected as the C-radical precursor. Functional groups like Boc protected amines, esters, ketones and acetals found in hecogenin (**3**n), tropine (**3**k) and epiandrosterone (**3**I) were tolerated by this protocol and good to excellent stereocontrol was achieved. For some examples, solubility issues were solved by addition of either DMAc or 1,3-dioxane (see SI).



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Scheme 3. Deoxygenative borylation of tertiary alkyl oxalates *via* reductive C-O bond cleavage. Reaction conditions: **4a-n** (0.2 mmol), B₂cat₂ (0.6 mmol), Ir(ppy)₃ (1.0 mol%), DMF (0.6 -1.2 mL), rt, 24 h; pinacol (0.8 mmol), Et₃N (0.7 mL), 1h, isolated yields. [a] The relative stereochemistry could not be assigned; ^areaction was performed on a 1.0 mmol scale.

We next searched for a suitable activating group for the deoxygenative borylation of tertiary alcohols. Due to undesired side reactions, xanthates are not eligible *tert*-alkyl radical precursors and oxalates were selected instead.^[10] Oxalates have been used in combination with Barton-PTOC esters (PTOC = pyridine-2-thione-N-oxycarbonyl) for *tert*-alkyl radical generation^[11] and recent examples also documented the feasibility of a reductive cleavage of alkyl oxalates using either activated Zn in a Ni promoted process or a strongly reducing photocatalyst at elevated temperatures^[8].

We chose the readily prepared methyl oxalate 4a as model substrate and C-radical generation was tested using photoredox catalysis. To our delight, formation of product 5a was observed with fac-Ir(ppy)₃ (tris[2-phenylpyridinato- C^2 ,N]iridium(III)) as the catalyst. Optimization of the reaction conditions revealed DMF to be the ideal solvent (see SI) and the alkyl boronic ester 5a was obtained in 85% isolated yield (Scheme 3). Various tert-alkyl boronic esters could be prepared in good to excellent yields by using this protocol (5b-e). Internal alkenes may be tolerated as documented by the transformation of α -terpineol to 5f, which represents a valuable building block in organic synthesis. Furthermore, benzylic amines and esters are tolerated (see 5g and 5i). When the 1,3-dioxolane protected ketone 4h was used as the substrate, partial deprotection was observed during the reaction, likely do to the presence of the Lewis acidic B₂cat₂. Therefore, the product was fully deprotected upon treatment of the product mixture with catalytic quantities of NaBAr^F₄ (sodium tetrakis(3,5-trifluoromethylphenyl)borate) in water^[12] to give the ketone 5h in good yield (71%). The reaction also proceeds well for benzyl methyl oxalates as exemplified by the preparation of 5j (79%). However, non-activated sec-alkyl methyl oxalates are not good substrates for this deoxygenative borylation. For example, boronic ester 3a was prepared in low 25% yield using the oxalate route (see SI). At 1.0 mmol scale, 5a was obtained in 77% yield documenting the robustness of the process.

We were very pleased to find that tertiary propargylic alcohols can be converted *via* this strategy with complete regiocontrol to allenyl boronic esters, that are highly valuable reagents for the synthesis of homopropargylic alcohols and amines.^[13a,b] Notably, this process represents the first radical approach towards this important compound class.^[13a,ce] Branched propargylic alcohols performed well and the boronic esters **5k-m** were isolated in 57-67% yield. The reaction was also applied to biologically active mestranol to provide the allene **5n** in 54% yield. Unfortunately, substituted alkynes targeting tetrasubstituted allenes led to complex reaction mixtures.

The suggested mechanism for the photoredox process is presented in Scheme 4A. The alkyl radical **A** gets generated by electron transfer from photoexcited $Ir(ppy)_3$ catalyst ($Ir(III)^*$) to the methyl oxalate **4** and subsequent C–O bond cleavage. **A** then adds to B₂cat₂ to give adduct radical **B**, which is trapped by the solvent to intermediate **C**.^[2h] The weak B–B one electron σ -bond

readily homolyzes to give the alkyl catechol boronic ester 5 along with **D**. Radical **D** is oxidized by the photocatalyst (Ir(IV)) leading to cation E thereby regenerating Ir(III). The proposed mechanism for the non-chain radial TTMSS-process is depicted in Scheme 4B (method A). The radical nature of these transformations was supported by a radial probe experiment (cyclopropane ring opening, see SI). The TTMSS-radical, generated from the silane by hydrogen atom transfer to a 2-cyano-isopropyl radical derived from AIBN, reacts with xanthate 1 in an addition fragmentation sequence to give radical A and (Me₃Si)₃SiSCOSMe. Radical A gets borylated via B and C as described before. The radical D is eventually oxidized by another 2-cyanoprop-2-yl radical leading to E. Due to the stability and also the nucleophilicity of radical D, its direct reduction by TTMSS is likely an inefficient step, explaining the necessity of using a stoichiometric amount of AIBN. The mechanism of the light-mediated borylation with TTMSS (method B) remains unclear.



Scheme 4. Proposed reaction mechanisms for the radical borylation of xanthates, O-thionocarbamates and methyl oxalates.

In conclusion, two novel approaches for the radical borylation of secondary and tertiary alcohols *via* their xanthates, O-thionocarbamates or methyl oxalates were introduced. For secondary alcohols, a metal-free protocol using TTMSS as a radical mediator was developed. For tertiary alcohols, where xanthates and its derivatives cannot be accessed, deoxygenative borylation can be achieved *via* their methyl oxalates using Ir-photordeox catalysis without any additional radical mediator. These processes deliver a great variety of alkyl boronic esters in good to excellent yields under mild conditions. Importantly,

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propargylic alcohols are converted with complete regioselectivity to the corresponding allenyl boronic esters, that are valuable reagents in organic synthesis.

Acknowledgements

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O to B! Two different approaches for the deoxygenative borylation of secondary and tertiary alcohols are introduced. These processes proceed *via* radical intermediates and product boronic esters are obtained in good to excellent yields.

 $\begin{array}{c} R \\ R' \\ R'' \\ R'$